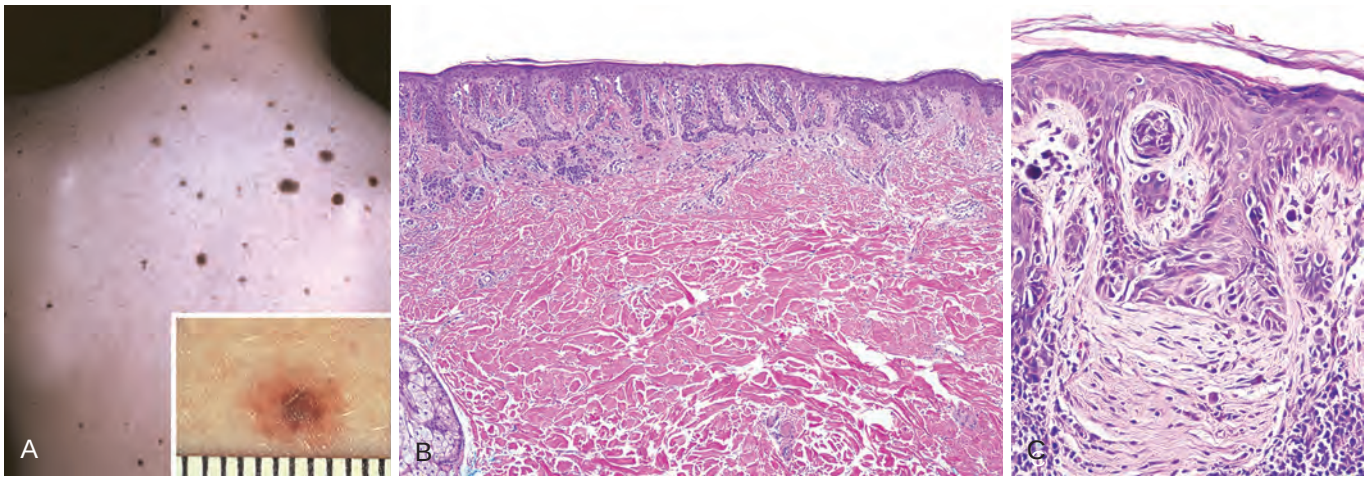

Figure 25-6 Dysplastic nevus. **A,** Numerous atypical nevi on the back. **B,** One such lesion (*inset A*) has a compound nevus component (*left*) and an asymmetric junctional nevus component (*right*). The former corresponds to the more pigmented and raised central zone and the latter to the less pigmented, flat peripheral rim of the lesion shown in **A. C,** An important feature is the presence of cytologic atypia (irregularly shaped, dark-staining nuclei). The dermis underlying the atypical cells characteristically shows linear, or lamellar, fibrosis.

hundreds in those with the dysplastic nevus syndrome (Fig. 25-6*A*). They are flat macules, slightly raised plaques with a "pebbly" surface, or target-like lesions with a darker raised center and irregular flat periphery. They can be recognized by their size, variability in pigmentation (variegation), and irregular borders. Most seem to be acquired rather than congenital. Unlike ordinary moles, dysplastic nevi occur on both sun-exposed and protected body surfaces.

Microscopically, dysplastic nevi usually involve both the epidermis and the dermis and exhibit architectural and cytologic atypia (Fig. 25-6*A, B*). **Nevus cell nests within the epidermis may be enlarged and often fuse or coalescence with adjacent nests.** As part of this process, single nevus cells begin to replace the normal basal cell layer along the dermoepidermal junction, producing **lentiginous hyperplasia.** Cytologic atypia takes the form of nuclear enlargement, irregular, often angulated, nuclear contours, and hyperchromasia (Fig. 25-6*C*). Associated alterations in the superficial dermis include lymphocytic infiltrates (usually sparse); release of melanin from dead nevus cells into the dermis (**melanin incontinence**), where it is phagocytosed by dermal macrophages; and a peculiar **linear fibrosis** surrounding the epidermal rete ridges that are involved by the nevus. The diagnosis is based on this constellation of features, rather than any single finding.

Melanoma

Melanoma is the most deadly of all skin cancers and is strongly linked to acquired mutations caused by exposure to UV radiation in sunlight. Melanoma is a relatively common neoplasm that can be cured if it is detected and treated when it is in its earliest stages. The great preponderance of melanoma arises in the skin; other sites of origin include the oral and anogenital mucosal surfaces (i.e., oropharynx, gastrointestinal and genitourinary tracts), esophagus, meninges, and the uvea of the eye (Chapter 29). The following comments apply to cutaneous melanomas.

Today, as a result of increased public awareness of the signs of cutaneous melanoma, most are cured surgically. Nevertheless, the reported incidence of melanoma is increasing; more than 76,000 cases and more than 9,700 deaths are expected in the United States in 2014.

Pathogenesis. About 10% to 15% of melanomas are inherited as an autosomal dominant trait with variable penetrance; as mentioned when discussing dysplastic nevi, some of these familial cases are associated with germline mutations affecting the genes that regulate cell-cycle progression or telomerase (described later). The overwhelming majority of melanoma is sporadic and is related to a single predisposing environmental factor: ultraviolet radiation (UVR) damage from sun exposure. UVR is associated strongly with DNA damage. Consistent with a pathogenic role in this disease, sequencing of melanoma genomes has demonstrated a very high rate of point mutations that bear the signature of the damaging effects of UV radiation on DNA. In line with this molecular evidence, melanomas most commonly arise on sun-exposed surfaces, particularly the upper back in men and the back and legs in women, and lightly pigmented individuals are at higher risk than are darkly pigmented individuals. Other inherited genetic variants linked to a modestly increased risk of melanoma in fair-skinned populations act by diminishing melanin production in skin, thus presumably increasing the amount of damage that sun-exposure wreaks on melanocytes.

Nevertheless, the relationship between sun exposure and melanoma is not as straightforward as with other skin cancers (discussed later). Some studies suggest that periodic severe sunburns early in life are the most important risk factor. Furthermore, since melanomas sometimes occur in dark-skinned individuals and at body sites that are not sun-exposed, sunlight is not always an essential predisposing factor, and other environmental factors may also contribute to risk.

The most frequent "driver" mutations in melanoma affect cell cycle control, pro-growth pathways, and telomerase. Some of the more common mutations are as follows:

- *Mutations that disrupt cell cycle control genes.* The *CDKN2A* gene is mutated in approximately 40% of pedigrees with